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THE PROBLEM OF STRUCTURAL ANALYSIS OF BIOLOGICAL RHYTHMS

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16. Abstract

Several patterns in the adaptation reaction of the human body when stimuli are applied at various rhythms are studied. Electron microscopy, autoradiography and histochemistry are used for a structural analysis of adaptation reactions of the body at the intracellular level.

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THE PROBLEM OF STRUCTURAL ANALYSIS OF BIOLOGICAL RHYTHMS

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Investigation of the mechanisms of the body's adaptation to environmental factors is the central problem in clinical and experimental medicine. An important aspect of the problem but one, nevertheless, still attracting little attention of researchers is study of the interrelations between the disintegration and synthesis of materials (structures) in the course of adaptational reactions. Inseparably linked with each other, these processes take place at molecular, organoid (subcellular) and cellular levels, providing for the performance of specific functions and compensation of spent structures, i.e. physiological regeneration in the broad sense. Under normal conditions these opposite beginnings of the life process are in a state of relative equilibrium. Physiological and pathogenic stimuli alter it as the result of predominant intensification or inhibition of disintegration or synthesis which, in turn, entails a corresponding change in the activity of the opposite process directed toward restoration of the disturbed equilibrium. In essence it is this reaction which underlies the body's adaptation to a particular agent. /3*

Modern methods of morphological study — electron microscopy, autoradiography, histochemistry — are expanding the possibilities of structural analysis of adaptation processes and are making possible more accurate observation of their dynamics. Greatest attention in this article is given to several regularities in the adaptation reaction of the body under conditions of various rhythms of a stimulus. By the term "rhythm" in the future we shall mean repetition of some phenomenon or other after certain intervals of time.

A situation when the rhythm of an action changes while its dosage remains constant is suitable for showing the dynamics of variations in adap-

* Numbers in margin indicate pagination of original foreign text.

tation processes, i.e. their ability to reorganize under various environmental conditions. Regular studies based on this model were begun not long ago, however, already data have been obtained indicating high lability of biosynthetic processes during changing rhythms of pathogenic effects (D. S. Sarkisov and B. V. Vtyurin, 1967; D. S. Sarkisov et al., 1969, 1972).

Fig. 1 shows curves of DNA synthesis in liver tissue of mice, one group of which (b) was injected with CCl_4 once a week, another (c) — twice a week, and the third (d) — daily. Single doses of the toxic substance were constant, only the rhythm of injections changed.

Daily autoradiographic tests of DNA synthesis in liver tissue for 30 days showed that its intensity increased in conformity with the increased frequency of the stimulus. Analysis of the curves indicates, first of all, a sharp increase in the general level of synthetic activity of liver tissue and, secondly, /4 and this must be especially emphasized, an order in this synthetic activity where individual parts of the organ (cells) begin to "work" in the same rhythm. It is known that in normalcy DNA synthesis in different cells of an organ is nonsynchronous (I. A. Alov). The curves in Fig. 1 show that under experimental conditions rhythms of synthetic processes are synchronized in individual cells, which must be considered mobilization of the material resources of the organ for the most effective resolution of its most important problem at the moment — restoration of disturbed homeostasis. This is also expressed in the coordination of the new rhythm of peaks of synthetic activity of the organ (developed under these conditions) with that of the stimulus: with the injection of CCl_4 once a week the cycle of peaks of DNA synthesis in the liver appear once a week, with more frequent injections they correspondingly become more frequent and higher and, finally, with the most intense effect (daily injections) synthetic processes increase sharply; however, the organ can, evidently, no longer produce a clear "rhythm of resistance" and it becomes disordered and chaotic (see Fig. 1, d).

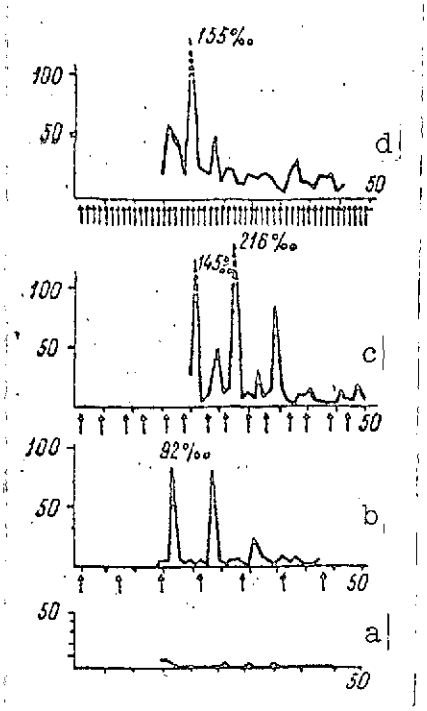

Figure 1. Dynamics of DNA synthesis in liver tissue with various rhythms of injections of CCl_4

a — control; b — once a week; c — twice a week; d — daily injections of CCl_4.

Horizontally — days of the test. Arrows indicate days of CCl_4 injections; vertically — index of labeled hepatocytes (in %).

These observations lead to the following conclusion: the intensity of synthetic processes varies, depending on the frequency of the pathogenic stimulus. The body forms rhythms of peak activity of synthetic processes that exactly follow each regular effect of the toxic agent and thereby largely negate it. This high lability of the life process is its universal characteristic which enables the body to preserve the equilibrium between disintegration and synthesis of materials and maintain homeostasis in continuously changing environmental conditions.

What are the structural manifestations of adaptation variations in the intensity of synthetic processes? Morphological studies show that they consist, first of all, in a change in the number of actively functioning structures. At the organ level this is expressed in the varying intensity of the function of its component parts, for example, hepatic lobules, various fields of mucosa of the stomach and the pancreas, individual groups of nephrons, muscle bundles, etc. At the cellular (tissue) level this principle is followed by "putting into operation" individual cells or, on the other hand, by eliminating them from active participation in the work.

In connection with the development of electron microscopy studies, the theory that in a state of relative rest only part of the cells in an organ are active (Barkroft) has received further substantiation.

It has been established that the ultrastructural equivalent of a state of functional rest in the cell is a thick network of endoplasmatic reticulum, a large number of ribosomes in its membranes, mitochondria with a dense osmiophilic matrix and regularly-arranged cristae, a compact hyperchromic nucleus, etc. Because of the large number of organoids in cytoplasm and the density of hyaloplasm and the matrix of mitochondria, those energetically charged, ready-for-work cells are distinguished as darker than the others in electron microscope studies. Intensive functional activity is accompanied by increased consumption of structures: the dark cell begins to "lighten." Mitochondria swell, their matrix clears, the canals in endoplasmatic reticulum are dilated, the number of ribosomes is reduced, hyaloplasm clears and swells, chromatin and the nucleolus migrate to the nuclear membrane. Later this light cell is cut off from activity and as the result of physiological regeneration of ultrastructures is again transformed into a dark cell, etc. These continuous variations in in the degree of functional activity of cells (dark ⇆ light) have already been described in various organs and tissues. It has been found that, for example, as the physical load on the myocardium increases, the number of light cells is correspondingly increased and the number of dark cells is decreased, which indicates gradual inclusion of cellular elements into the general work of the organ (P. Ya. Mul'diyarov, B. V. Vtyurin). Similar changes are found in neurons in one of their most important sections — synaptic apparatus during increased excitation (conversion of "dark" synapses to "light")(A. A. Manina; O. M. Pozdnyakov). Pyknotically-altered dying cells also darken. As this phenomenon is not related to the problem at hand, we shall not discuss it here. At the cellular level the increase of synthetic processes can be expressed not only in the activation of an ever-increasing number of cells, but also in their increased division.

We can now say with sufficient justification that the principle of continuous change in the number of actively functioning structures retains its place as the most important mechanism responsible for fluctuations in the synthetic activity of living systems at the intracellular level as well. If within the organ this principle is expressed in varying functional activity of its major parts, for example, within the acinus of the pancreas — in the intensive function of some cells and a state of relative rest in others — then within each individual cell it appears as functional heterogeneity of ultrastructures (B. V. Vtyurin; K. S. Mitin). Electron microscope and histochemical studies indicate that, evidently, in an active state at any given moment is only a part of cellular ultrastructures, for example, mitochondria. This is seen in their structural heterogeneity, in the presence of "dark" and "light" mitochondria similar to the above-described dark and light cells. The actively functioning mitochondrium swells, its matrix clears, the length of its cristae is reduced and the mitochondrium becomes "light;" then in the course of physiological regeneration it again "darkens" etc. Electronohistochemical studies indicate with sufficient basis that this principle of functional heterogeneity can be applied to even smaller structures, in particular to elements of organiods; in mitochondria, for example, at any given moment, only some structures (crista, matrix, etc.) can be found in an active state. A series of data obtained with the use of modern methods of morphological study indicate that there is, evidently, a whole range of various degrees of functional activity of the cell. This is provided by the continuous change in the total number of its ultrastructures in an active state at any given moment. This is indicated, for example, by the gradual increase in the number of "light" (swollen) i.e. actively functioning mitochondria in muscle cells of the heart in proportion to the increased severity and duration of physical loads. N. K. Permyakov et al., studied adaptational changes in the secretory cycle of acinic cells of the pancreas at the ultrastructural level and showed that their dynamics and intensity vary, depending on the diet.

The main role in studying structural bases of biological rhythms and, in particular, in quantitative analysis of the intensity of biosynthetic processes is played by electron autoradiography. Using this method, A. A. Pal'tsyn and /6

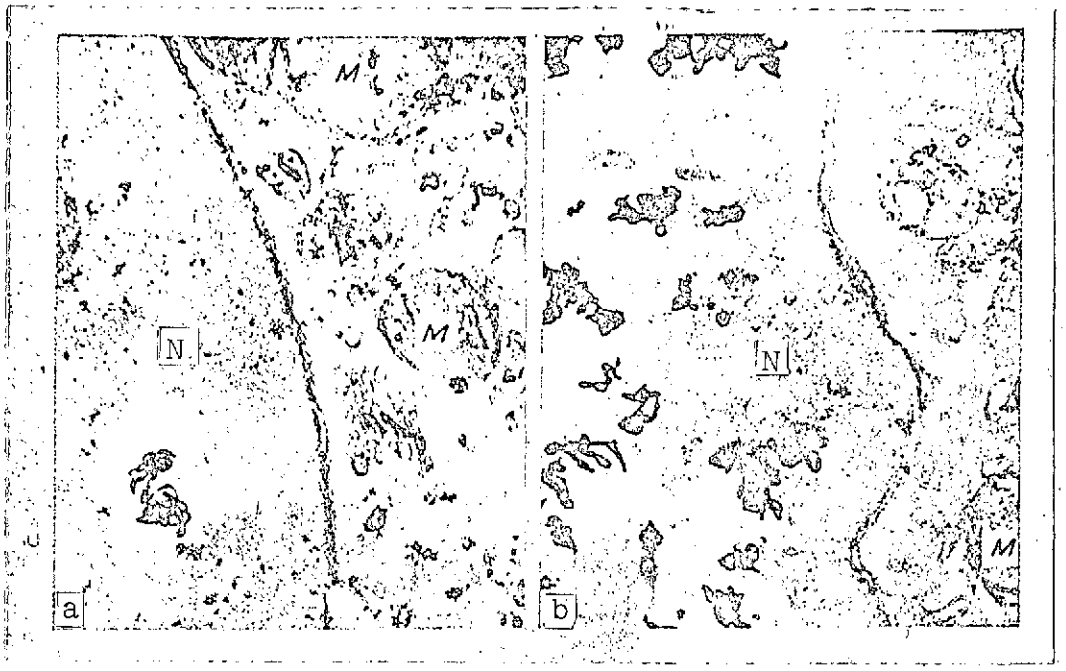

Figure 2. Increased DNA synthesis in liver tissue under the effect of CCl_4. Electron autoradiography. X35,000.

a — control. On hepatocyte nucleus — a single grain of silver; b — test. A large number of grains of silver on the cellular nucleus of a mouse which had received CCl_4. N — nucleus; M — mitochondria.

B. V. Vtyurin showed that if grains of silver are, as a rule, observed only singly or not at all on hepatocyte nuclei of control mice, in animals which have received CCl_4 several liver cells are seen in one field of view with a large number of grains of silver on the nuclei (Fig. 2). This increased DNA synthesis in hepatocytes is, as is known, a material basis for the development of cellular (mitosis) and intracellular (polyploidization of nuclei, hyperplasia of ultrastructures) regeneration of liver tissue.

The increase of synthetic processes in cells is accompanied not only by actuation of an ever-increasing number of ultrastructures (which are in a state of rest), but also by an increase in the number of the latter , their hyperplasia. V. S. Paukov and B. V. Vtyurin showed that under prolonged functional

strain in muscle tissues of the heart the number of mitochondria, ribosomes and myofibrils is increased, there is hyperplasia of Golgi apparatus and the endoplasmatic network, etc. Hyperplastic processes occur not only at the level of organoids (increased number), but also "within" the latter, expressed, for example, in the appearance of significantly larger-than-usual mitochondria. Hyperplasia of ultrastructures leads to hypertrophy of the cell — a phenomenon known since the last century, but only now receiving detailed morphological interpretation. The complex of intracellular adaptation reactions is not limited to these intracellular changes — activation of an ever-increasing number of ultrastructures and their hyperplasia. A third component consists of adaptational changes in cellular metabolism. If, for example, the liver regenerates after traumatic injury, the newly-formed tissue does not obviously differ essentially from lost tissue. A different result is observed with re- /7
generation after certain toxic effects. The well-known fact of the increased resistance of cells to repeated pathogenic effects indicates that tissue is being regenerated which differs from its predecessor; it is characterized, despite its morphological similarity, by new physiological features. The latter, evidently, have their own structural base located at the macromolecular, close to biochemical level, developed specifically "against" a certain agent and relating to corresponding changes in the enzyme system. Therefore, a new, extremely important problem arises — that of compensatory-adaptational reactions in enzyme systems of the cell as one of the main components of its general reparative reaction. Studies in this direction have only just begun.

For example, it is noted that in heart muscle cells around an infarct complex reorganization of metabolic processes occurs of a compensatory-adaptational character (A. I. Strukov et al., K. M. Danilova et al.). T. N. Drozd established that in patients with ulcers there is an adaptational change in the phases of activity and relative functional rest of liver tissue; this is the basis of rhythmic changes in the metabolism of hepatocytes — the Embden-Meyerhof-Krebs cycle periodically alternates with the pentose-phosphate cycle. A similar adaptational compensatory reaction at the level of enzyme systems was noted by A. G. Ufim-

tseva and V. V. Serov in kidney epithelium during various pathogenic effects. Of basic importance in this respect is the observation of L. A. Tiunov et al., who established that intensification of the rhythm of reparative regeneration of the liver with more frequent injection of a hepatotoxic agent (furfural) is accompanied by a corresponding intensification of the synthesis of several adaptive enzymes, in particular, increased activity of xanthinoxidase, which is responsible for the metabolism of aldehydes. With daily injection of the drug, the activity of this enzyme was significantly increased, while with less frequent injections it did not significantly differ from that in control animals. Thus, the rhythm of intracellular regenerator processes has a direct bearing on the induction of enzymes and conformation changes in protein molecules (M. G. Kritsman and A. S. Konikova).

The change in the number of actively functioning structures, noted above, is inherently connected with increased or weakened tempo of their restoration, i.e. regeneration. Therefore, it can be stated that adaptational changes in the intensity of synthetic processes are accompanied by corresponding changes in the rate of regeneration. From that it follows that variations in the activity of reparative processes can be used as morphological characteristics of biological rhythms. Of basic interest in this respect is intracellular regeneration. This is because the dynamics of cellular restoration (mitotic cycles) do not reflect the periodicity of functions directly, but indirectly, on the basis of changes which occur from time to time in large working blocks — cells, within which biochemical processes are already unfolding. In contrast, intracellular (molecular and ultrastructural) regeneration is directly responsible for a function, it is its structural equivalent. Therefore, the morphologist, observing variations in the intensity of physiological intracellular regeneration, approximates those ideal conditions when he can see the "picture" of the function. We must especially emphasize that in some organs (myocardium, central nervous system) mitotic division is lacking and, therefore, in interpreting structural bases of biological rhythms we must be oriented exclusively to the

kinetics of intracellular restoration. The significance of this is difficult to overestimate if we consider the importance of studying the periodicity of functional variations in the central nervous system as the chief apparatus of integrating internal biorhythms of the body with environmental rhythms.

It is evident from this that the most important practical conclusion from this view of intracellular regenerator processes is the prospect of detailed /8
structural analysis of cyclic variations in function. The first results of studies in this direction, noted above, lead to the following general conclusion: one of the most important properties of adaptational intracellular reactions is the lability of the rhythm of physiological regeneration of ultrastructures, i.e. the ability of cells to change the intensity of their consumption and new formation, depending on the frequency and force of external and internal environmental factors, and thereby equalize the rates of these two opposite processes.

Analyzing this remarkable ability of the body, we must take into consideration that a certain rhythmicity characterizes not only various environmental factors, but also the vital processes themselves, which are usually called "biological rhythms." From that it follows that in the interaction of the body with the environment there is a sort of overlaying of "external" rhythms on "internal" ones, and the result of such summation is finally determined by the physiological state of various organs and tissues. In this respect homeostasis is seen as a continuous balancing of rhythms of biological processes with those of numerous and varied effects on the body. Such a general-theoretical solution to the problem of adaptation of the body has already been given by I. M. Sechenov who wrote: "...the living machine is run by two kinds of impulses: changes arising in the machine itself in its operation and impulses arriving from without." The physical aspect of this problem was later substantially developed by Soviet researchers, especially N. Ye. Vvedenskiy and A. A. Ukhtomskiy. The main result of these studies, in which the object of investigation was the nervous system, was establishment that summation of the rhythm of a stimulus with intrinsic rhythms of biological systems is not mechanical superimposition, but a complex integral process.

The essence of the latter is that a living system, in particular the cell, falling under the influence of a certain rhythm of an external effect, reorganizes its own rhythm of metabolic processes so that it begins to correspond to that of the effect, "to agree" with it. Thanks to this ability, figuratively called by A. A. Ukhtomskiy the ability of cell rhythm to "adopt" external effects, homeostasis is preserved and the necessary level of functional activity strictly maintained.

We must especially point out that only with such an understanding will the problem of biological rhythms attain importance for clinical medicine and, in particular, for further study of the regularities and mechanisms of compensatory-adaptational reactions of the body. Nevertheless, for many years this problem has been developed unilaterally, primarily in study of the fluctuation of vital body functions. Deeper structural analysis of biological rhythms is hindered by the fact that until recently methodological resources for such study were limited to the cellular level and, therefore, it was reserved almost exclusively to study of mitotic cycles of various organs. This did not allow the morphologist to record faster intracellular rhythms which are "closer" to function (indicated above). But now, with the rapid development of cytological methods of study, they have received little use in long tests to trace the dynamics of adaptation reorganization of intracellular biorhythms in connection with changing rhythms of external effects.

The main attention of researchers is still focused on /9
solving such questions as the dynamics of the formation, accumulation and migration of materials from the nucleus to the cytoplasm (Ströcker et al.; Leblond and Amano; Levy; Prescott; Amano et al., and others), investigating the mechanisms of this migration through the nuclear membrane (Gallan and Tomlin; Altmann; Wischnitzer, Koshiba et al.), analysis of the process of accumulation and consumption of various materials in the nucleus and cytoplasm in single effects of various factors (Noorduyn and de Man; Pogo and Littan: I. Stein and O. Stein; Citoler and de Leon).

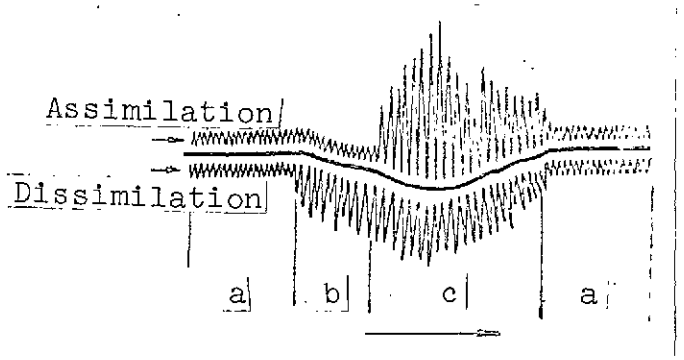

Figure 3. Schematic drawing of the ratios of disintegration and synthesis of materials (structures) at various stages of the pathological process.

a — physiological regeneration; b — dystrophy → necrosis; c — reparative regeneration.

There is no doubt about the importance of these cytological studies but they are only indirectly related to the problem of biological rhythms in the situation indicated above. Nevertheless, a number of electron microscope studies of intracellular adaptation processes in the myocardium (V. P. Tumanov; P. Ya. Mul'diyarov; B. V. Vtyurin), liver (L. A. Tiunov et al., D. S. Sarkisov et al.) and pancreas (N. K. Permyakov et al.) already quite clearly indicate that the concepts advanced by the school of I. M. Sechenov (N. Ye. Vvedenskiy, A. A. Ukhtomskiy) about the "lability" and "adoption" by cell rhythm of external effects are structurally justified; the application of these concepts is not limited to just the nervous system, but extends to the activity of cells and all other organs, acquiring the importance of a general-biological rule.

On the basis of the above data on molecular pathology today a rather complete concept can be formulated about the general dynamics of changes in cells during various pathological processes, in particular, about the physiological intracellular restoration of structures, based on these changes. Even though there is no doubt about the paramount importance of physiological regeneration in vital activities of the body and it has always been emphasized in textbooks

on general pathology and pathological anatomy, the lack of an inherent connection between the concepts of regularities in the continuous restoration of structures of the organism on one hand and such phenomena as dystrophy, necrosis and reparation on the other is noteworthy. Current data on regularities in intracellular restoration dictate the following scheme of cellular changes during various pathological processes (Fig. 3). The main process underlying the entire range of structural and functional changes in cells is considered to be the establishment of a relative equilibrium between disintegration and synthesis of protein (structures). It determines physiological regeneration at various levels — molecular, organoid and cellular. We consider equilibrium between these processes as the normal state of cells and tissues (see Fig. 3, a, physiological regeneration). The effect of a pathogenic stimulus is expressed in an "upset" of this balance, which can consist, for example, of a disturbance of mechanisms responsible for the synthesis of protein (enzyme disease), a sharp increase in the consumption of material resources in extreme degrees of functional stress and so forth. In all these cases the equilibrium between the rate of disintegration of structures and the intensity of their regeneration is disturbed in favor of the former. We record this "negative balance" of physiological regeneration in the form of swelling of mitochondria, vacuolization of the endoplasmatic reticulum, reduction of the number of ribosomes and other ultrastructures, decrease in the amount of glycogen, the appearance of fat inclusions and vacuoles, granularity of cytoplasm and we call it "dystrophy" (in sense of damage) (see Fig. 3, b). The latter, therefore, is the result of disturbances to physiological regeneration at molecular and ultrastructural levels. If the process continues in this "unfavorable" direction and the disproportion between destruction and synthesis (regeneration) continues to grow, necrosis appears, i.e. an extreme disturbance of physiological regeneration. /10

However, in many cases in response to sharply increased disintegration of protein the cell is able, to a corresponding degree, to increase anabolic processes and return the rhythm of restoration of its material resources to the limits of physiological regeneration. This period of sharp increase in synthetic processes is expressed morphologically by an increased number of

ultrastructures, their hyperplasia and hypertrophy and increased mitotic activity; we use the term "reparative regeneration: (see Fig. 3, c).

Molecular pathology data, therefore, reveal in the complex picture of cellular changes a common, pivotal biological process, variants of which comprise the aggregate of symptoms which "externally" seem different to us. This pivotal process is physiological regeneration, i.e. the strictly balanced restoration of living matter. Its disturbance toward predominance of disintegration gives a picture of dystrophy and the related adaptation increased synthesis — reparative regeneration. Therefore, dystrophy and reparative regeneration, in the final analysis, are two antagonistic deviations of physiological regeneration from its "normal" course. Therefore, when we speak of physiological regeneration, dystrophy, reparative regeneration, etc., we are dealing not with clearly limited forms of cellular reaction to an external effect and not with various general pathological phenomena, but with variants and phases of one biological process — assimilation and dissimilation of living matter. The inherent connection between physiological and reparative regeneration and the necessity of considering them as variants of the same synthetic reaction of the body have been noted repeatedly by A. N. Studitskiy (1952, 1963). Reparative regeneration, therefore, must not be considered as a concluding step in the pathological process: from the very start of a pathogenic stimulus and the attendant disturbance of physiological regeneration the mechanism which increases reproductive processes is activated but it stands out especially clearly at the end of the disease when dystrophy predominates.

Conclusion

The comprehensive use of modern methods of morphological study — electron microscopy, autoradiography and histochemistry — makes possible structural analysis of adaptation reactions of the body at the intracellular level and thereby connects even closer morphological and biochemical aspects of this most important problem of clinical medicine. The most general, universal adaptative reaction of the cells in response to various stimuli is varying activity of bio-

synthetic processes, directed toward preserving the balance between disintegration and synthesis of materials (structures) and thereby maintaining the constancy of the body's internal environment. Manifestations of adaptive variations in the activity of biosynthetic processes are: 1) changes in the number of actively functioning structures from normal, 2) new formation, hyperplasia of structures (organoids, cells), 3) adaptive reorganization of enzyme systems. /11

Adaptive changes in the activity of biosynthetic processes, expressed in changes in the rate of restoration (regeneration) at molecular, organoid (ultrastructural) and cellular levels, are distinguished by high accuracy. With a rhythmic stimulus the organism rapidly forms its own corresponding rhythm of disintegration and synthesis of structures directed toward restoring the disturbed homeostasis and, therefore, neutralizing the effect of the pathogenic action. In a morphological sense the essence of this adaptive reorganization of biological rhythms is that with various changes in the frequency of the stimulus, the intensity of reparative reaction is each time established at a level preventing a deficit of structures which would be incompatable with life. Continuous compensation of the rhythms of various effects on the body by its own rhythms of vital activity is one of the specific expressions of the principle of the unity between the organism and its environment.

REFERENCES

1. Alov, I.A. Tsitofiziologiya i patologiya mitoza (Cytophysiology and pathology of mitosis). Moscow,1972.

2. Barkroft, J. Osnovnye cherty arkhitektury fiziologicheskikh funktsiy. (Basic features of the architecture of physiological functions). Moscow-Leningrad, 1937.

3. Vayl', S.S. Trudy Leningradsk. ob-va patologoanatomov (Works of the Leningrad society of pathological anatomists). Leningrad, Vol. 13, 1972. p. 218.

4. Vvedenskiy, N.Ye. Izbrannye proizvedeniya (Selected works). Moscow, Ch. 2, 1951.

5. Vtyurin, B.V. Nekotorye voprosy funktsional'noy morfologii ul'trastruktur miokarda. (Some questions of functional morphology of ultra-

structures of the myocardium). Doctoral dissertation. Moscow, 1969.

6. Davydovskiy, I.V. Obshchaya patologiya cheloveka (General human pathology). Moscow, 1961, p. 33.

7. Danilova K. M., M.I. Klibaner and V.N. Baranov. Arkh. pat., Vol. 1, 1970, p. 29.

8. Drozd, T.N. Funktsional'naya morfologiya pecheni pri yazvennoy bolezni (Functional morphology of the liver in cases of ulcers). Candidate's dissertation, Moscow, 1972.

9. Kritsman, M.G. and A.S. Konikova. Induktsiya fermentov v norme i patologii (The induction of enzymes in normalcy and pathology). Moscow, 1968.

10. Manina, A.A. Ul'trastrukturnye izmeneniya i reparativnye protsessy v tsentral'noy nervnoy sisteme pri razlichnykh vozdeystviyakh (Ultrastructural changes and reparative processes in the central nervous system under various effects). Leningrad, 1971.

11. Mitin, K.S. Submikroskopicheskaya morfologiya serdtsa pri infarkte miokarda (Submicroscopic morphology of the heart in myocardial infarct). Doctoral dissertation. Moscow, 1969.

12. Mul'diyarov, P.Ya. Ul'trastruktura miokarda pri razlichnykh rezhimakh fizicheskoy nagruzki (Ultrastructure of the myocardium in various physical load regimes). Candidate's dissertation. Moscow, 1967.

13. Pal'tsyn, A.A. and B.V. Vtyurin. Byull. eksper. biol. med. No. 12, 1972, p. 99.

14. Paukov, V.S. Ul'trastruktura gipertrofirovannogo miokarda u cheloveka i v eksperimente (Ultrastructure of hypertrophied myocardium in man and in experiment). Candidate's dissertation. Moscow, 1968.

15. Permyakov, N.K., A.Ye. Podol'skiy and G.P. Titova. In the book: Materialy 5-go Vsesoyuzn. s"yezda patologoanatomov (Material of the 5th All-Union Congress of Pathological Anatomists). Moscow, 1971, p. 31.

16. Pozdnyakov, O.M. Strukturno-funktsional'nye vzaimootnosheniya v normal'nom i povrezhdennom nervno-myshechnom sinapse (Structuro-functional interrelations in the normal and damaged neuro-muscular synapse). Doctoral dissertation. Moscow, 1972.

17. Sarkisov, D.S. and B.V. Vtyurin. In the book: Materialy konderentsii po patologii kletki In-ta morfologii cheloveka AMN SSSR (Materials of the conference on cellular pathology of the Institute of Human Morphology, USSR Academy of Medical Sciences, Moscow, 1967, p. 10.

18. Sarkisov, D.S., L.D. Krymskiy, K.V. Botsmanov, et al. Arkh. pat. Vol. 3, 1969, p. 22.

19. Sarkisov, D.S., L.D. Krymskiy, K.V. Botsmanov, et al. Byull. eksper. biol. No. 5, 1972, p. 113.

20. Sarkisov, D.S. and B.V. Vtyurin. Elektronnomikroskipicheskiy analiz povysheniya vynoslivosti serdtsa (Electron microscope analysis of increased resistance of the heart). Moscow, 1969.

21. Sechenov, I.M. Avtobiograficheskiye zapiski (Autobiographical notes), Moscow, 1945, p. 172.

22. Strukov, A.I., Ye.F. Lushnikov and K.A. Gornak. Gistokhimiya infarkta miokarda (Histochemistry of myocardial infarct). Moscow, 1967.

23. Studitskiy, A.N. Izv. AN SSSR. Seriya biol., No. 6, 1952, p. 6.

24. Studitskiy, A.N. Zh. obshchey biol., Vol. 4, 1963, p. 241.

25. Tiunov, L.A., G.A. Vasil'yev and L.V. Ivanova. Byull. eksper. biol., No. 9, 1970, p. 29.

26. Tumanov, V.P. Nekotorye zakonomernosti povysheniya vynoslivosti miokarda (Some regularities in increased resistance of the myocardium). Candidate's dissertation, Moscow, 1967.

27. Ufimtseva, A.G. Gistofermentokhimiya nefrona v norme i patologii (Histoenzymochemistry of the nephron in normalcy and pathology) Candidate's dissertation. Moscow, 1971.

28. Ukhtomskiy, A.A. Sobraniye sochineniy (Collected works). Leningrad, Vol. 5, 1954, p. 92.

29. Altmann, H.W. Klin. Wschr., Vol. 33, 1955, p. 306.

30. Amano, M., C.P. Leblond and N. Nadler. Exp. Cell. Res., Vol. 38, 1965, p. 314.

31. Citoler, P. and F. de Leon. Verh. dtsch. ges. Path., Vol. 53, 1969, p. 341.

32. Gallan, H. and S. Tomlin. Proc. Roy. Soc. B., Vol. 137, 1950, p. 367.

33. Koshiba, K., K. Smetana and H. Busch. Exp. Cell. Res., Vol. 60, 1970, p. 199.

34. Leblond, C.P. and M.J. Amano. Histochem. Cytochem. Vol. 10, 1962, p. 162.

35. Levy, H.B. Proc. Soc. exp. Biol. (N.Y.), Vol. 113, 1963, p. 886.

36. Noorduyn, N. and J. de Man. J. cell. Biol., Vol. 30, 1966, p. 655.

37. Pogo, A.O. and V.C. Littan. Proc. nat. Acad. Sic. (USA), Vol. 57, 1967, p. 743.

38. Prescott, D.M. In the book: Progress in Nucleic Acid Research and Molecular Biology. London, Vol. 3, 1964, p. 33.

39. Serov, W.W. Fourth Internat. congress of Histochem. and Cytochem. Kyoto, 1972, p. 287.

40. Stein, O. and J. Stein. J. cell Biol., Vol. 33, 1967, p. 319.

41. Ströcker, E., W. Maurer and H. Altmann. Naturwissenschaften, Vol. 48, 1961, p. 582.

42. Wischnitzer, S. J. Ultrastruct. Res.. Vol. 1, 1958, 201.

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